Remarks

In view of the above amendments and the following remarks, reconsideration of the outstanding office action is respectfully requested.

Applicant has amended claims 68, 73, and 77 without prejudice. Claims 68 and 71-77 remain pending. Descriptive support for the amendments to claim 68 appear at pages 17-18.

The rejection of claims 68 and 71-76 under 35 U.S.C. § 112 (first paragraph) as containing new matter is respectfully traversed in view of the above amendments.

The rejection of claims 68 and 71-77 under 35 U.S.C. § 112 (first paragraph) as lacking written descriptive support is respectfully traversed in view of the above amendments and the following remarks.

The U.S. Patent and Trademark Office ("PTO") has maintained its position that the disclosure of three biliverdin reductases ("BVRs") and encoding polynucleotides is an insufficient representation of all mammalian BVR. While applicant respectfully disagrees, applicant submits that the specification clearly supports that applicant was in possession of mammalian BVR characterized by being encoded by nucleic acid sequences whose complements hybridize to the nucleotide sequences of SEQ ID NO: 2 or 5 under the recited hybridization and wash conditions.

As demonstrated by the previously submitted Declaration of Mahin D. Maines under 37 C.F.R. § 1.132 ("Maines Decl.") (submitted with response filed March 3, 2004), a high degree of structural similarity and functional conservation exists between the three BVR proteins identified in the present application as well as two others identified in the Maines Declaration (Maines Decl. ¶¶ 4–11 and exhibits cited therein). Based upon the high degree of structural similarity of the three BVR proteins identified in the present application (confirmed by their high degree of structural similarity with mouse and pig BVR sequences and the functional similarity of many mammalian BVR proteins), persons of skill in the art would have understood that applicants were in possession of mammalian BVR proteins that are structurally and functionally conserved with those identified by sequence in the present application. In view of the above amendments and the evidence of record, applicant submits that written description exists for use of the mammalian BVR as presently claimed.

For these reasons, applicant submits that the rejection of claims 68 and 71-77 is improper and should be withdrawn.

The rejection of claims 68 and 71-77 under 35 U.S.C. § 112 (first paragraph) for lack of enablement is respectfully traversed in view of the above amendments and the following remarks.

The PTO has asserted three bases for the rejection of these claims, including (i) enablement of all mammalian BVR, (ii) enablement of fragments other than SEQ ID NOS: 18, 19, 34, and 35 that are generically encompassed by SEQ ID NO: 16 or 17, and (iii) enablement of *in vivo* methods of practicing the claimed invention. The second basis is rendered moot by the above amendments; therefore only the first and third bases of rejection are addressed below.

With respect to the first basis of rejection, applicant submits that the rejection is overcome by the above amendments to claim 68. In particular, given the recitation of sequence identifiers and hybridization conditions that thereby define the structural relatedness among nucleic acid molecules encoding the recited mammalian BVR, applicant submits that a person of skill in the art is fully able to use other mammalian BVR or fragments thereof, as presently recited, in practicing the claimed invention. Given the high degree of structural and functional conservation among mammalian BVR, persons of skill in the art are fully able to isolate other BVR sequences (as applicant has done with pig BVR) and utilize them in the presently claimed invention (*see* Maines Decl. ¶¶ 7, 9, 11).

With respect to the second basis of rejection, applicant submits herewith a Third Declaration of Mahin D. Maines Under 37 C.F.R. § 1.132 ("Third Maines Decl.") in support of the position that the *in vitro* results are predictive of *in vivo* success, as demonstrated by the results presented in the Third Maines Decl.

Dr. Maines transfected 293 cells with either (1) an empty vector (pCDNA3), (2) a vector capable of inducing human BVR expression (pCDNA3-BVR), or (3) a retroviral construct containing small interference fragments for BVR (si-BVR). Third Maines Decl. ¶ 5. The transfected cells were starved overnight with growth media containing 0.1% FBS. Id. Cells were than treated with 100 nM phorbol-12-myristate-13-acetate ("PMA") for 20 min and lysed with buffer containing: 20 mM MOPS, 50 mM β-glycerophosphate, 50 mM NaF, 1 mM Na Vanadate, 5 mM EGTA, 2 mM EDTA, 1% NP-40, 1 mM dithiothreitol, 1 mM benzamidine, 1 mM phenylmethanesulphonylfluoride (PMSF), 10 μg/ml leupeptin and aprotinin. Id. Cell lysates were sonicated, centrifuged 15 min at 13 krpm, and supernatants

were processed for determination of protein content by using Bradford assay and for determination of PKC activity by using ELISA kit from Stressgen. Id. The results of the Bradford assay allowed for quantitation of proteins present in the lysates sample obtained from the transfected cells, which allowed for normalizing the ELISA results discussed below. Third Maines Decl. ¶ 6. PMA is a known activator of protein kinase C, both *in vivo* and *in vitro*. Third Maines Decl. ¶ 7. As expected, the introduction of PMA showed an increase in PKC activity for each transfection (i.e., comparing each transfection with and without PMA). Id. The effect of BVR on *in vivo* PKC activity is clearly demonstrated, because the BVR-transfected cells displayed a substantial increase in PKC activity both with and without PMA. Id. Given the consistency between the *in vitro* results reported in Example 3 of the present application and the *in vivo* results described above, persons of skill in the art would expect that other *in vitro* results described in Example 3 would likewise predict the same or similar outcomes for *in vivo* modification of PKC activity. Third Maines Decl. ¶ 8.

The PTO has previously acknowledged that the specification sufficiently describes delivery of BVR into cells *in vivo*. *See* Paper No. 12 at p. 10; office action dated September 3, 2003, at p. 10. Thus, because the specification teaches one of skill in the art how to practice the present invention *in vivo* and the *in vitro* results of Example 3 are predictive of *in vivo* success for modifying activity of PKC *in vivo*, as confirmed by the data presented in the Third Maines Decl., the present application fully enables persons of skill in the art to practice the claimed invention.

For all these reasons, the rejection of claims 68 and 71-77 for lack of enablement is improper and should be withdrawn.

In view of all of the foregoing, applicant submits that this case is in condition for allowance and such allowance is earnestly solicited.

Respectfully submitted,

Date: January 13, 2005

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Laura L. Trost